REMARKS

Claims 34-37, 42-45, 66-69, 77, and 80-88 are pending in the application. Claims 80-84 are withdrawn as being drawn to non-elected inventions. Claim 79 has been canceled without prejudice or disclaimer. Claims 34-37, 42-45, 66-69, 77, 79, and 85-88 are under active consideration.

Claims 34, 42, 66, 77, and 85 have been amended to recite a polypeptide comprising (a) amino acid residues 384 to 661 of an HCV-1 polyprotein; or (b) the corresponding residues of other HCV isolates; or (c) a sequence having at least about 90% sequence identity to (a) or (b). Support for the amendments can be found in the specification, for example, at page 9, lines 18-24; page 15, lines 20-25.

Claims 37, 45, 69, and 88 have been amended to recite nucleotide sequences comprising at least about 90% identity to each other. Support for the amendments can be found in the specification, for example, at page 15, lines 20-25.

Claims 34, 37, 42, 45, 66, 69, 77, 85, and 88 have been amended to recite an immunogenic polypeptide or fusion protein comprising an HCV epitope. Support for the amendments can be found in the specification, for example, at page 11, line 22 through page 12, line 2; page 22, lines 25-26; page 26, lines 27-29.

Claim 77 has been amended to incorporate the limitations of now canceled claim 79. As amended, claim 77 recites an immunogenic polypeptide comprising (a) amino acid residues 384 to 661 of an HCV-1 polyprotein; or (b) the corresponding residues of other HCV isolates; or (c) a sequence having at least about 90% sequence identity to (a) or (b), wherein said polypeptide is capable of eliciting an immunological response against HCV.

Claim 87 has been amended to recite the substantially complete S domain of the second HBsAg recited in claim 85.

The present amendments do not introduce new issues or new matter, and place the subject application in condition for allowance and/or simplify issues for appeal. Accordingly, entry of the amendments is proper and respectfully requested.

Cancellation and amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce

in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the canceled or unamended claims.

Applicants note with appreciation the withdrawal of the previous rejections under 35 U.S.C. § 101, 35 U.S.C. § 112, first paragraph, 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 103.

35 U.S.C. § 112, first paragraph, Written Description

Claims 34, 35, 37, 42, 43, 45, 66, 67, 69, 77, 79, and 85-88 have been rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of an adequate written description.

The Final Office Action alleges that "[t]here is no description in the application of any non-HCV sequence that is capable of inducing an anti-HCV immune response, or any identification of any structure that would [be] capable of inducing such a response" (Final Office Action, page 4). and that "[t]he art indicates that the 80% homology limitation is not a structural characteristic that corresponds to the presence of the required function (as would be the case where an epitope is shared with an HCV polypeptide)" (Final Office Action, page 5).

Applicants respectfully traverse the rejections under 35 U.S.C. § 112 first paragraph and the Office's purported facts underlying the rejection on the following grounds.

The fundamental factual inquiry in written description is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. *See, e.g., Vas-Cath, Inc.*, 935 F.2d at 1563-64, 19 USPQ2d at 1117. Determining whether the written description requirement is satisfied is a question of fact and the burden is on the Examiner to provide evidence as to why a skilled artisan would not have recognized that the applicant was in possession of claimed invention at the time of filing. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim,* 191 USPQ 90 (CCPA 1976).

It is not necessary that the application describe the claimed invention *in ipsis verba.* Rather, all that is required is that the specification reasonably convey possession of the invention. *See, e.g., In re Lukach,* 169 USPQ 795, 796 (CCPA 1971).

The Patent Office's own guidelines on written description are clear -- the written description requirement is highly fact-dependent and there is a strong presumption that an adequate written description of the claimed invention is present at the time of filing. The test is whether the specification contains sufficient disclosure regarding structural and functional characteristics of the claimed sequences to satisfy the written description requirement.

The specification as filed for the present application more than adequately describes the structure and function of the claimed nucleic acid sequences. The pending claims recite both the structure (*e.g.*, a nucleic acid molecule which encodes the sequence of amino acid residues 384 to 661 of an HCV-1 polyprotein, the corresponding residues of other HCV isolates; or a sequence having at least about 90% sequence identity thereto; or a nucleic acid molecule comprising the sequence of SEQ ID NO:6, nucleotides 1992 through 3584 of SEQ ID NO:6, or a sequence having at least about 90% sequence identity thereto) and function (elicits an immune response against HCV) of the recited nucleic acids. Although the presence of an HCV epitope is implicit in the recitation that a polypeptide elicit an immune response against HCV, the claims have been amended to specifically recite that the immunogenic polypeptide or fusion proteins, encoded by the recited nucleic acids, comprise an HCV epitope. Therefore, when properly construed, it is plain that only nucleic acid sequences having the recited structure and function are encompassed by the pending claims.

Given the information provided by the sequence of the HCV-1 polyprotein, one of skill in the art would be able to routinely identify a nucleic acid encoding the sequence of amino acid residues 384 to 661 of the HCV-1 polyprotein, the corresponding residues of other HCV isolates; or a sequence having at least about 90% sequence identity thereto. Similarly, given the information provided by the sequence of SEQ ID NO:6, one of skill in the art would be able to routinely identify a nucleic acid comprising the sequence of nucleotides 1992 through 3584 of SEQ ID NO:6 or a sequence having at least about 90%

sequence identity thereto. See the specification, for example, on page 15, line 29 through page 16, line 30, where it is noted how to determine sequences falling within the requisite percent identity. At the time of filing of the instant application, determining sequence identity was routine. Furthermore, numerous sequences from different HCV strains that can be used in the practice of the invention are described in the specification, for example, at page 22, lines 2-15 and page 25, lines 1-16. The specification also provides guidance on methods of identifying nucleic acids that encode an immunogenic polypeptide capable of eliciting an immunological response against HCV. See the specification, for example, at Examples 1-5, which describe assays for detection of the expressed antigen (*e.g.*, page 38), detection of viral-like particles containing the expressed antigen (*e.g.*, pages 39-40), and measurement of antibody titers in response to nucleic acid immunization (*e.g.*, pages 41-42).

The claims, as amended, recite nucleic acid molecules encoding fusion proteins comprising a polypeptide "capable of eliciting an immunological response against HCV." A correlation between polypeptide structure (primary sequence or tertiary structure) and immunogenic function indicates that immunogenic polypeptides can tolerate many modifications. Sequences that do not encode an immunogenic polypeptide that elicits an immune response against HCV are not encompassed by the claims.

In the case at hand, a skilled artisan reading the specification would have known that Applicants were in possession of claimed nucleic acids as recited in the claims in view of the specification's extensive disclosure of (1) precise sequences falling in the scope of the claims; (2) conventional, known methods of aligning nucleic acids or polypeptides; and (3) conventional, known methods of testing polypeptides for HCV antigenicity (i.e., sequences comprising an HCV epitope). In view of the disclosure of the specification and state of the art and the amendments to the claims, it would have been plain to the skilled artisan that Applicants were in possession of the claimed invention at the time the specification was filed.

Applicants further direct the Examiner's attention to the Patent Office's own guidelines regarding the written description requirement. Example 14 of the Patent Office's "Synopsis of Application of Written Description Guidelines" is

clear that a **single** disclosed species may be representative of a "product-by-function" genus when all members exhibit structural identity to a reference compound (here, HCV-1 polyprotein or SEQ ID NO:6) and when an assay is provided for identifying all variants having the claimed activity (such as detailed in the specification, for example, at pages 41-42). From Example 14 of the US PTO written description Guidelines:

> ... The procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art. ....
>
> There is actual reduction to practice of a single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO:3. The **single species disclosed** is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

Like Example 14, applicants in the pending case have provided a limit to the structural identity (90% identity), a specified activity of the variants (encode polypeptide that is capable of eliciting an immunological response against HCV) and methods for identifying constructs exhibiting the specified activity (See, *e.g.*, immunoassay described at pages 41-42 of the application). Therefore, as in PTO Example 14, the multiple species disclosed in the application are representative of the genus as a whole.

Accordingly, one of skill in the art would conclude applicant was in possession of the necessary common attributes possessed by the members of the genus, and it is clear that, as concluded in PTO Example 14 of the Written Description Guidelines, the present application provides adequate written description for the substance of claims 34, 37, 42, 45, 66, 69, 79, 85, and 88.

For at least the above reasons, withdrawal of the written description rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

35 U.S.C. § 112, second paragraph

Claims 77 and 87 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Final Office Action, pages 6 and 7). In particular, the Final Office Action alleges:

> [C]laim 79 has now been added to the application. This claim depends from claim 77, and purports to narrow the claim to embodiments wherein the HCV polypeptide has at least about 80% identity to an HCV sequence, and is capable of inducing an immune response against HCV, but does not require the presence of an actual HCV sequence. Claims 85-88 have similar language. In view of the addition of new claims 79 and 85-88, it is not clear what the extent of the term "an HCV immunogenic polypeptide" is. (Final Office Action, page 6).

In addition, the Final Office Action alleges that claim 87 is indefinite because "there are two substantially complete S domains in claim 85, and while it appears that the claim intends to refer to the S domain present in the fusion protein, claim 87 does not clearly state as such" (Final Office Action, page 7).

Applicants respectfully traverse the rejections under 35 U.S.C. § 112 second paragraph and the Office's purported facts underlying the rejection on the following grounds.

Claim 77 has been amended to incorporate the limitations of now canceled claim 79. As amended, claim 77 recites an immunogenic polypeptide that comprises (a) amino acid residues 384 to 661 of an HCV-1 polyprotein; or (b) the corresponding residues of other HCV isolates; or (c) a sequence having at least about 90% sequence identity to (a) or (b), wherein said polypeptide is capable of eliciting an immunological response against HCV.

Claim 87 has been amended to state that the substantially complete S domain is of the second HBsAg recited in claim 85.

For at least these reasons, Applicants respectfully request that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

35 U.S.C. § 103

A. Rejection based on Major in view of Michalak and Valenzuela

Claims 34-36, 42-44, and 66-68 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Major et al. (J. Virol. 69:5798-5805; hereinafter "Major") in view of the reference of Michalak et al. (J. Gen. Virol. 78:2299-2306; hereinafter "Michalak") and further in view of Valenzuela et al. (Bio/Technology 3:323-326; hereinafter "Valenzuela (1)").

Applicants respectfully traverse the rejections under 35 U.S.C. § 103 and the Office Action remarks and purported facts underlying the rejection on the following grounds.

The claims are directed to nucleic acids encoding a fusion protein comprising a substantially complete S domain of HBsAg and (a) a polypeptide comprising amino acid residues 384 to 661 of an HCV-1 polyprotein or (b) the corresponding amino acids of other HCV isolates or (c) a sequence having at least 90% identity to (a) or (b).

The primary reference, Major, was cited for teaching the use of a nucleic acid encoding an HBsAg and an HCV E2 fusion protein for DNA based vaccination against HCV (See Office Action of July 29, 2005 at page 7, where it is asserted that Major teaches the use of a nucleic acid encoding an E2 protein for DNA based vaccination against HCV.").

Michalak was cited as a secondary reference that disclosing that a truncated form of E2 **protein** was recognized by antibody that binds only to properly folded E2.

Valenzuela 1 was cited for teaching the successful expression of a fusion protein comprising the HBV S protein.

Based on the primary reference of Major and the secondary references of Michalak and Valenzuela 1, the Examiner has asserted that a person of skill in the art would have had a reasonable expectation of success in using the claimed combination. The Examiner notes that Valenzuela demonstrated **success** in the expression of a fusion protein...with a **similar** length to that of the fusion that would result from the

combination of Major and Michalak." *Id.*; *emphasis added*). Based on these observations, the Examiner has asserted that one would have had a reasonable expectation of success based on the "**success** in inducing anti-HCV responses using a **similar** fusion protein. "Office Action of July 29, 2005; *emphasis added*

As previously pointed out in Applicants' response dated October 31, 2005, Major **does not** teach or suggest a nucleic acid encoding HBsAg and HCV E2. Major teaches a nucleic acid encoding HBsAg and a portion of HCV "core" or "capsid" antigen.

In response to this apparent misinterpretation of the disclosure in Major, the Examiner has responded that "...the reference does not indicate that fusions of the HBsAg and E2 **would be unable** to induce anti-HCV immune responses...[and that]...the teachings in Major indicate that fusions comprising E2 may only have limited operability, but **do not indicate that those in the art would have had no motivation** for the construction of such fusion proteins." (Final Office Action of January 13, 2006 at page 8; *emphases added*).

In response to the above observations, it is respectfully submitted that Major does not teach or suggest a fusion comprising E2 and HbsAg.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." M.P.E.P. § 706.02.

Major describes **nucleic acids** encoding an HBsAg fused to an HCV nucleocapsid polypeptide. Major does not teach or a suggest nucleic acid encoding any type of fusion comprising an HCV E2 antigen.

Michalak describes truncated forms of HCV E1 and E2 **proteins** having C-terminal deletions. Nowhere does Michalak describe or suggest a **nucleic acid** encoding such E1 or E2 antigens fused to any HBV sequence.

Valenzuela pertains to immunization against herpes simplex virus utilizing a vector expressing a hybrid particle comprising HBsAg and herpes simplex virus surface antigens. Valenzuela fails to describe or suggest immunization using HCV antigens. The

claims are directed to nucleic acids encoding a fusion protein comprising a substantially complete S domain of HBsAg and a polypeptide comprising amino acid residues 384 to 661 of an HCV-1 polyprotein or the corresponding amino acids of other HCV isolates or a sequence having at least 90% to (a) or (b).

Therefore, no combination of the cited references teaches or suggests all of the limitations of claims 34-36, 42-44, and 66-68.

Even assuming, arguendo, that the combination of references describe in combination a nucleic acid encoding E2 polypeptide fused to HBsAg there is still no motivation provided to combine the individual elements as claimed. The motivation to combine the references cannot derive from Major, which does not suggest making any constructs encoding fusions of HBsAg with E2 antigens for any purpose. In particular, Major does not teach or suggest any constructs encoding a fusion of HBsAg with amino acid residues 384 to 661 of an HCV-1 polyprotein.

Furthermore, Michalak cannot provide the requisite motivation to produce nucleic acids encoding fusions of HCV E2 with HBsAg, as claimed, because Michalak is silent as to fusions of E2 with any HBV antigen, let alone HBsAg. The Examiner points to the solubility of truncated forms of E2 protein for the motivation to combine the references (Final Office Action, page 8). However, the solubility of a truncated form of E2 does not provide motivation to combine an E2 antigen with HBsAg in a fusion protein.

The remaining references are entirely silent with regard to HCV fusions. Thus, there is no motivation to combine their methods with the E2 antigens described by Michalak. Simply put, the references do not provide the requisite motivation to combine their teachings as set forth in the Final Office Action.

In the absence of some teaching or suggestion in the cited references concerning nucleic acids encoding fusion proteins comprising a substantially complete S domain of HBsAg and a polypeptide comprising amino acid residues 384 to 661 of an HCV-1 polyprotein; as described in the present application, the Examiner has presented no more than an improper hindsight reconstruction of the present invention.

B. Rejection of claims based on Jacobs in view of Major, Michalak, and Valenzuela

Claim 77 remains rejected and new claim 79 is now also rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Jacobs et al. (U.S. Patent No. 6,306,625; hereinafter "Jacobs") in view of Major et al., Michalak et al. and Valenzuela et al. as applied to claims 34-36, 42-44, and 66-68. Jacobs is cited for teaching the use of HBsAg as a carrier molecule for other antigenic sequences, the fusion of such antigenic sequences to the N-terminus of the S protein sequence, cell lines comprising nucleic acids encoding chimeric antigens in combination with nucleic acids encoding only HBsAg, and the production from such cell lines of HBsAg particles comprising chimeric antigens. Applicants respectfully traverse the rejection under 35 U.S.C. § 103 and the remarks and purported facts underlying the rejection on the following grounds.

Claim 77 is directed to a cell line that expresses a virus-like particle (VLP) comprising a first HBsAg and a chimeric antigen, wherein the chimeric antigen comprises a second HBsAg which is linked to an immunogenic polypeptide, and wherein the first and the second HBsAg each comprise a substantially complete S domain, wherein said immunogenic polypeptide comprises (a) amino acid residues 384 to 661 of an HCV-1 polyprotein; or (b) the corresponding residues of other HCV isolates; or (c) a sequence having at least about 90% sequence identity to (a) or (b), wherein said polypeptide comprises an HCV epitope and is capable of eliciting an immunological response against HCV.

Jacobs fails to describe any cell line producing VLPs containing a chimeric antigen comprising an HCV immunogenic polypeptide. Nor does Jacobs overcome the deficiencies noted above for Major, Michalak and Valenzuela. None of the references of Major, Michalak, and Valenzuela teach or suggest a cell line expressing virus-like particles comprising HBsAg in addition to a chimeric antigen comprising HBsAg linked to an HCV immunogenic polypeptide. Therefore, no combination of the cited references teaches or suggests all the limitations of claim 77.

C. Rejection of the claims based on Jacobs in view of Major, Michalak, and Valenzuela, further in view of GenBank Accession Numbers X02763 and M62321

Claim 37 remains rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Jacobs et al. in view of Major et al., Michalak et al. and Valenzuela et al. as applied to claim 77, and further in view of GenBank Accession Numbers X02763 and M62321. The Examiner asserts that the sequence of nucleotides 1564-2241 of X02763 corresponds to the sequence of nucleotides 2907-3583 of SEQ ID NO:6, coding for HBsAg, and that the sequence of nucleotides 1491-2324 of M62321 corresponds to the sequence of nucleotides 2067-2900 of SEQ ID NO:6, coding for a portion of the HCV E2 protein. Applicants respectfully traverse the rejection under 35 U.S.C. § 103 and the remarks and purported facts underlying the rejection on the following grounds.

Claim 37 is directed to a nucleic acid molecule comprising nucleotides 1992 through 3584 of SEQ ID NO:6, or a nucleotide sequence having at least about 90% sequence identity thereto that is capable of expressing a fusion protein that comprises an HCV epitope and elicits an immunological response against HCV.

No motivation can be found in any of the cited references for combining the two sequences of X02763 or M62321 to produce SEQ ID NO:6 as suggested by the Final Office Action. As discussed above, none of the cited references teach or suggest a nucleic acid encoding a fusion comprising HBsAg and an HCV E2 antigen. X02763 and M62321 do not disclose or suggest any construct encoding such a fusion. In particular, X02763 and M62321 fail to disclose or suggest the 75 nucleotides from 1992 to 2066 of SEQ ID NO:6 or the 6 nucleotides of SEQ ID NO:6 forming the "linker" between the end of the M62321 sequence and the beginning of the X02763 sequence. Therefore, no combination of the cited references teaches or suggests all the limitations of claim 37.

D. Jacobs in view of Major, Michalak, and Valenzuela (1), further in view of De Wilde, Valenzuela (2), and Mountford

In addition, new claims 85-87 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Jacobs et al. in view of Major et al., Michalak et al. and Valenzuela et al., as applied to claim 77, and further in view of the references of De Wilde et al. (U.S. Patent No. 5,928,902; hereinafter "De Wilde"), Valenzuela et al. (U.S. Patent No. 4,722,840; hereinafter "Valenzuela (2)"), and Mountford et al. (Proc. Natl. Acad. Sci. U.S.A. 91:4303-4307; hereinafter "Mountford"). De Wilde is cited for teaching that hybrid particles form between hybrid HBsAg proteins and native HBsAg protein when host cells are co-transformed with nucleic acids encoding both the native and the hybrid HBsAg proteins. Mountford is cited for teaching the use of a viral IRES to induce the expression of two proteins in the same transformation vector. In particular, the Office Action alleges:

> From these teachings, it would have been obvious to those in the art to use such a combined vector for the expression of both the native and the hybrid genes required for the production of the hybrid particles suggested by the previously cited references in combination with the 840 patent and De Wilde. Thus, the combined teaches suggest the use of hybrid particles comprising both a HBsAg and a chimeric HBsAg fused to an HCV E2 protein, and the making of expression vectors encoding such proteins for expression in mammalian cells. From the successful expression and formation of hybrid particles in each of Jacobs, De Wilde, and the 840 patent, and the successful coexpression in Mountford, those of ordinary skill in the art would have had a reasonable expectation of success. (Final Office Action, pages 11-12.)

Applicants respectfully traverse the rejection under 35 U.S.C. § 103 and the remarks and purported facts underlying the rejection on the following grounds.

Claims 85-87 are directed to vectors comprising a nucleic acid sequence which encodes a first HBsAg and a nucleic acid sequence which encodes a fusion protein comprising a second HBsAg which is linked to an immunogenic polypeptide, wherein the first and the second HBsAg each comprise a substantially complete S domain; and wherein the immunogenic polypeptide comprises (a) amino acid residues 384 to 661 of an HCV-1 polyprotein; or (b) the corresponding residues of other HCV isolates; or (c) a sequence having at least about 90% sequence identity to (a) or (b), wherein said

polypeptide comprises an HCV epitope and is capable of eliciting an immunological response against HCV.

As discussed above, Major, Michalak, and Valenzuela (1) fail to teach or suggest any nucleic acid encoding a fusion protein comprising HBsAg and an HCV E2 antigen. None of the cited references teach or suggest a vector comprising a nucleic acid sequence which encodes HBsAg in addition to a nucleic acid sequence which encodes a fusion protein comprising HBsAg linked to an HCV immunogenic polypeptide.

De Wilde pertains to immunization against malaria infection, and accordingly, teaches a hybrid protein comprising the CS protein of *P. falciparum*. De Wilde fails, however, to teach any nucleic acid encoding a fusion of HBsAg to any HCV immunogenic polypeptide, nor does De Wilde provide any motivation for using any HCV antigen.

Valenzuela (2) similarly fails to disclose or suggest any nucleic acid or vector encoding a chimeric antigen comprising HBsAg linked to an HCV immunogenic polypeptide.

Mountford merely describes bicistronic constructs in general and has nothing to do with expression of HCV fusions or VLPs. Therefore, no combination of the cited references teaches or suggests all the limitations of claims 85-87. Furthermore, none of these references cures the deficiencies of Major et al. as discussed above.

It is axiomatic that statements in the prior art must be considered in the context of the teaching of the entire reference, and that rejection of claims **cannot** be predicated on mere identification in a reference of individual components of claimed limitations. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. *See, e.g., In re Kotzab* 217 F.3d 1365, 55 USPQ2d 1313, 1317 (CAFC 2000, emphasis added):

While the test for establishing an implicit teaching, motivation or suggestion is what the combination of these two statements [in the reference] would have suggested to those of ordinary skill in the art, the two statements cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection **cannot** be predicated on the mere identification [in the reference] of

individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

Virtually all inventions are combinations of elements that can be individually identified in multiple references. See, e.g., *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998) noting that the Office cannot rely on a high level of skill in the art to overcome the differences between the selected elements in the references, it cannot rely on a high level of skill in the art to provide the necessary motivation; *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002), affirming that common knowledge and common sense are not the specialized knowledge and expertise necessary to establish a motivation to arrive at the claimed invention.

Thus, the requirement is not whether each claimed element can be identified individually in a reference but, rather, whether the Examiner can show "reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet*, 47 USPQ2d at 1458. In the pending case, the Office has not met this burden.

As explained in Section 2143.01 of the MPEP, the mere fact that references can be combined or modified does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Since the suggestion or motivation to combine the references to arrive at the claimed invention is not in the references, the Examiner is required to cite to some knowledge generally available to one of ordinary skill in the art for the motivation to combine the references. (MPEP2143). It is respectfully submitted that the Examiner has not provided such knowledge. Instead, the Examiner has asserted that because (1) Major teaches a nucleic acid encoding a fusion protein comprising HBsAg and an HCV antigen (*i.e.*, nucleocapsid) and (2) Michalak teaches that a truncated form of E2 comprising residues 384-661 "is the best candidate for a soluble form" of E2, it would have been obvious to combine the two to produce a construct encoding a fusion of HBsAg and an E2 antigen.

If the rejection is maintained, applicant requests clarification regarding the Examiner's position, either in the form of scientific literature, or by a declaration pursuant to 37 CFR §1.104(d)(2).

Without a suggestion to modify the references evident in the prior art, as well as a lack of a reasonable expectation of success, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). As also stated by the Court of Appeals for the Federal Circuit "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). Therefore, the Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103.

For at least the above reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

Michael J. Moran
Novartis Vaccines & Diagnostics
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662-8097
Tel: (510) 923-2969
Fax: (510) 655-3542

Respectfully submitted,

Date: July 13, 2006

By: Jenny Bushbinder

Jenny Bushbinder, Ph.D.
Registration No. 48,588
(650) 354-3383

Novartis Vaccines & Diagnostics
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662-8097